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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,995	12/14/2001	Robert L. Bratzler	C1037/7025(HCL/MAT)	7158

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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,995	BRATZLER, ROBERT L.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-8*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, claims 1-18 and SEQ ID NOS: 245-247, 261-263, 273, 300, 321 and 343 in Paper No. 12/18/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 53-74 have been canceled. Claims 1-18 are now pending in the present application.

3. Claims 1, 3-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are vague and indefinite in that the "antiangiogenic nucleic acid molecule" does not have a structure. What is this recitation intended to encompass?

4. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting angiogenesis in a subject in need of such treatment comprising administering to the subject one antiangiogenic nucleic acid molecule (ODN 1826, SEQ ID NO: 69) in an amount effective to inhibit angiogenesis in the subject, does not reasonably provide enablement for a method of inhibiting angiogenesis in a subject in need of such treatment comprising administering to the subject at least one antiangiogenic nucleic acid molecule in an amount effective to inhibit angiogenesis in the subject.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to methods of inhibiting angiogenesis in a subject in need of such treatment comprising administering to the subject at least one antiangiogenic nucleic acid molecule in an amount effective to inhibit angiogenesis in the subject. Dependent method claims are also directed to specific nucleic acid molecules (T-rich, poly G, CpG motif, etc) and the addition of other components (anticancer agent, antiarthritis agent, etc) in the administered composition.

The specification does not set forth any enablement for the ten sequences specifically elected or the more than 1000 sequences set forth in claim 2 with regard to inhibiting or reducing angiogenesis in a subject in need of such treatment. The independent claims are directed to a method that broadly encompasses administering a nucleic acid molecule to inhibit angiogenesis in a subject, while claims 2, 6, 16 and others specifically administer a CpG nucleic acid to inhibit angiogenesis in a subject. Applicant specifically elected ten sequences that are CpG nucleic acid molecules (SEQ ID NOS: 245-247, 261-263, 273, 300, 321 and 343), however the specification is not enabled for the claimed method using any of these elected sequences.

The specification teaches that angiogenesis is the process by which new blood vessels are formed; the overall driving factor for the process is the cells' need for oxygen and nutrients. Abnormal angiogenesis occurs when the body loses control of angiogenesis resulting in excessive or insufficient blood vessel growth. Ulcers, stroke and heart attacks result from the absence of angiogenesis normally required for natural healing. Excessive blood vessel proliferation can result in

tumor growth, tumor spread, blindness, psoriasis and rheumatoid arthritis. A neoplastic situation of pro- and anti-angiogenesis factors is skewed in favor of angiogenesis. Angiogenesis is necessary for continued growth of neoplasms and therefore is a direct correlation between extent of vascularization found in neoplasms and potential for metastasis.

The specification sets forth an example on page 56 of the claimed method. The specification example uses ODN 1826 (SEQ ID NO: 69). Mice were used. Mice of group 1 were given matrigel alone. Mice of group 2 were given matrigel, bFGF (basic fibroblastic growth factor) and heparin. Mice of group 3 were given matrigel, bFGF, heparin and ODN 1826. Mice of group 4 were given matrigel, bFGF and heparin as in group 2 and in addition this group of mice were given daily injections of ODN 1826 for 6 days. On day 6 all mice were euthanised and the matrigel plugs were collected. The hemoglobin and total protein content of the matrigel plugs was determined. The specification indicates that group 3 mice had a 2-fold decrease in the amount of hemoglobin present in the matrigel plugs when compared to group 2. The inclusion of a CpG ODN, specifically ODN 1826 (SEQ ID NO: 69) had a negative influence on angiogenesis (i.e. inhibition). Although group 4 received daily delivery of CpG (SEQ ID NO: 69) to the opposite flank from the matrigel plug, this did not appear to influence angiogenesis. The specification sets forth the possibility that CpG administered intravenously or subcutaneously in a region closer to the plug (an accordingly tumor mass) would manifest anti-angiogenic activity; CpG ODN may have to be present in the vicinity of active angiogenesis in order to have a negative influence (p. 59).

However, the state of the art indicates that CpG molecules induce angiogenesis, not inhibit angiogenesis (Zheng et al, PNAS USA, 2002,

99/13:8944-8949). Zheng et al teach that DNA containing bioactive CpG motifs induces angiogenesis (abstract). Zheng et al teaches that both CpG ODN and HSV DNA trigger new blood vessel formation (i.e. angiogenesis) and that this is mediated by VEGF production (p. 8944, col. 1; results, pp. 8945-8948; p. 8948, col. 1). Zheng et al teach that CpG motifs in HSV DNA may contribute to the angiogenesis characteristics of stromal keratitis (p. 8944, col. 1). "Current studies provide evidence that HSV DNA, likely through its content of bioactive CpG motifs, contributes to virus-induced ocular angiogenesis. The degree of angiogenesis elicited by HSV DNA and CpG ODN was 75% of that induced by the potent angiogenic factor VEGF." (p. 8948, col. 2). In view of the lack of the scope of enablement in the specification of the claimed invention and the state of the art with regard to the claimed invention indicating the opposite result would be achieved, it would require undue experimentation for one of skill in the art to practice the scope of the claimed method of inhibiting angiogenesis in a subject in need of such treatment comprising administering to the subject at least one antiangiogenic nucleic acid molecule in an amount effective to inhibit angiogenesis in the subject. The scope of the claimed invention is not enabled by the specification.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 1, 5-12 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Brysch et al (WO 95/17507).

Brysch et al disclose the use of said antisense nucleic acids and derivatives thereof for the manufacturing of a pharmaceutical composition for the treatment of neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis (abstract). Brysch et al disclose nucleic acids that are strong inhibitors of angiogenesis (p. 3). The prior art discloses that the nucleic acid sequence can be phosphorothioate derivatives (pp. 8-9). "The antisense-nucleic acid of the invention can be used as pharmaceutical composition or medicament. This medicament can be used for treating neoplasms and/or immune diseases and/or diseases involving pathological angiogenesis in which the expression of c-erbB-2 derived receptor protein or truncated $p185^{C\text{-}erbB2}$ is of relevance for the pathogenicity. It can be used to reduce neoplastic cell growth in cells expressing $p185^{C\text{-}erbB2}$ to reverse resistance of tumor cells to the immune-response, to inhibit pathological angiogenesis and to stimulate the immune system. The antisense nucleic acids of the invention are intermediate products of the pharmaceutical composition or medicament of the invention. The pharmaceutical composition may

comprise besides the effective compound(s) suitable carrier agents, solvents and other ingredients known in the art for producing medicaments. Preferably, these agents facilitate the administration of the pharmaceutical composition of the invention." (pp. 10-11) Brysch et al disclose that the immune response to a variety of neoplasms was significantly increased by the use of the antisense nucleic acids described below. Lymphocyte growth and activity was stimulated in co-culture assays culturing tumor cells and peripheral blood monocytes together. Furthermore, the antisense nucleic acids described above, also acted as inhibitors of angiogenesis (p. 12). Brysch et al discloses nucleic acid sequences that contain the CpG motif, are T-rich or poly G nucleic acid sequences, and the sequences are 8 to 100 nucleotides (see for example SEQ ID NO: 3, 10, 17, 24, 52, 61, 68, 70, 75, 81, 97, 99-101 and 106). The prior art discloses methods of inhibiting angiogenesis in a subject in need of such treatment comprising administering to the subject at least one nucleic acid molecule in an amount effective to inhibit angiogenesis in the subject.

The prior art anticipates the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicant's methods with the methods of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed methods and the methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

8. Claims 1, 3, 5-10, 13, 14 and 16-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Stein et al (6030955).

Stein et al disclose a method of inhibiting the formation of blood vessels (i.e. angiogenesis) in a subject which comprises administering to the subject an amount of a phosphorothioate oligonucleotide moiety of suitable length and base composition effective to inhibit VEGF molecules from binding to VEGF receptor (col. 2; col. 7; cols. 11-12; claims). A method of inhibiting proliferation of cells having a malignant phenotype in a subject comprising administering to the subject an amount of a phosphorothioate oligonucleotide moiety of suitable length is disclosed (col. 2). The treatment of cancers and tumors is disclosed using the oligonucleotides (col. 2; figures). Stein et al disclose the use of phosphorothioate oligonucleotide moieties, modifications of these oligonucleotides and that the length of the oligonucleotide has a length of 8 to 100 nucleotide residues (col. 5). Stein et al disclose that the oligonucleotide may be linked to other agents, cross-linkers, endonucleases, lipophilic carriers or peptide conjugates (col. 6). Stein et al discloses that "an antiangiogenic use describes those uses of the subject invention which result in the inhibition of the formation of blood vessels. An example of a situation in which a subject suffers from an antiangiogenic effect would be the subject suffers from a disease in which the disease causes an abnormal formation of blood vessels. The most common examples of such diseases include, but are not limited to arteriosclerosis, atherosclerosis, cancer, diabetic retinopathy, coronary thrombosis, and/or any disease resulting from neovascularization." (col. 7, l. 27-37; see also col. 7, l. 38-67) Stein et al disclose that the oligonucleotides can have the CG motif (see col. 8).

The prior art anticipates the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicant's methods with the methods of the prior art reference, the burden is upon applicants to show a

distinction between the material structural and functional characteristics of the claimed methods and the methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. No claims are allowed.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM

March 10, 2004